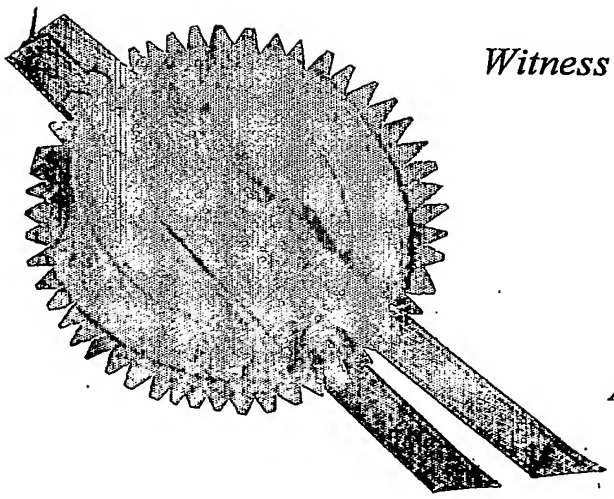
IB/04/2957

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1144/Del/2003*** *dated* ***12th September 2003.***



Witness my hand this 16th day of November 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

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DEL 03

12 SEP 2003

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR PRODUCTION OF CRYSTALLINE FORMS OF OXETANONE DERIVATIVE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. MOHAN PRASAD

c. KESHAV DEO

d. ANAND PANDEY

e. KILOL PATEL

f. SEEMA KANWAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, YATENDRA KUMAR, MOHAN PRASAD, KESHAV DEO, ANAND PANDEY. KILOL PATEL, SEEMA KANWAR of Ranbaxy Laboratories Limited. Plot No. 20. Sector – 18. Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India. all Indian Nationals. the true and first inventors for this invention or applicant in the convention country declare that the applicant herein. **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place. New Delhi - 110 019. India. is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b.

(MOHAN PRASAD)

c.

(KESHAV DEO)

d.

(ANAND PANDEY)

e.

(KILOL PATEL)

f.

(SEEMA KANWAR)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
- a. Complete Specification (3 copies)
- b. Drawings (3 copies)
- c. Priority document(s)
- d. Statement and Undertaking on FORM – 3
- e. Power of Authority (Not required)
- f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **12TH** day of **September, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

1144 DEL 03

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR PRODUCTION OF CRYSTALLINE FORMS OF OXETANONE DERIVATIVE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

A process for preparing a crystalline form II of orlistat, which is tetrahydrolipstatin, is provided. Further a process for preparing crystalline form I of orlistat from crystalline form II of orlistat, is provided.

Orlistat is a useful pancreatic lipase-inhibiting agents and can be used for the prevention and treatment of obesity and hyperlipaemia. Chemically, It is N-formyl-L-leucine[2S-[2alpha(R*),3 beta]]-1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester and is known from US patent US 4,598,089, in which the product is isolated as a waxy material.

Purification of orlistat by chromatographic method using toluene and ethyl acetate has been reported in several references such as US 4,983,746; *Helv. Chim. Acta.* 1987, 70, 1412; *J. Org.Chem.*, 1988, 53, 1218 and *J. Org. Chem.*,1993, 58,7768.

J. Chem, Soc. Perkin. Trans. I, 1998, 17, 2679 reports the use of hexane and ethyl acetate for chromatographic purification of orlistat to obtain the product as an amorphous solid.

Further, US 6,156,911; *Tetrahedron letters*, 1989, 30, 1833; *J. Org.Chem.*,1991, 56, 4714 and *Helv. Chim. Acta.* 1987, 70, 1412 disclose a crystalline form of orlistat, obtained by recrystallization with hydrocarbons such as hexane, pentane and heptane, and characterized it by melting point and infrared spectroscopy. For convenience this crystalline form is herein after called as form I.

Another crystalline form of orlistat, with unique X-ray diffraction pattern, is marketed by Roche as Xenical capsules but surprisingly, has not been reported anywhere. It is herein after called as form II.

The characteristic XRD, IR spectra and DSC graph of form I are given as figure 1, 2 and 3 respectively, as shown in the accompanied drawings. The characteristic XRD, IR spectra and DSC graph of form II are given as figure 4, 5 and 6 respectively, as shown in the accompanied drawings.

A process for preparing a crystalline form II of orlistat comprising crystallizating orlistat from diisopropyl ether is provided.

Further, a process for preparing the crystalline form I of orlistat comprising heating form II of orlistat till it melts and allowing it to cool, is provided.

The starting orlistat, to be used in the preparation of crystalline form II of orlistat, may be obtained as a solution directly from a reaction mixture in which orlistat is formed and used as such without isolation. Alternatively, form I, amorphous or waxy form of orlistat may be used.

Orlistat can be obtained by methods known in the art including US 4,598,089; US 4,983,746; US 6.156.911; US 5,412,110; US 2002110873; *Helv. Chim. Acta.* 1987, 70, 1412; *J. Org.Chem.*, 1988. 53. 1218; *J. Org.Chem.* 1993, 58, 7768; *J. Chem, Soc. Perkin. Trans. I*, 1998. 17. 2679; *Tetrahedron letters*, 1989, 30, 1833; *J. Org.Chem.* 1991, 56, 4714 and *Chem. Commun.*1999, 17, 1743.

In general, the crystallization is carried out by dissolving orlistat in diisopropyl ether, optionally concentrating the solution obtained, and cooling the solution till a precipitate is obtained, stirring at the same temperature till complete precipitation followed by filtration or centrifugation and drying. Precipitation may also be achieved without stirring.

The volume of diisopropyl ether to dissolve orlistat may be 2 to 10 volume by weight of orlistat.

Orlistat and diisopropyl ether may be stirred at room temperature or higher temperatures up to reflux temperature to get a clear solution.

The obtained solution may be cooled from about 5 to about -20°C to precipitate form II of orlistat.

The precipitate is filtered at the same temperature and dried at room temperature under reduced pressure.

The crystalline form II of orlistat is converted to crystalline form I of orlistat by heating to 40 to 45°C to get a melted syrup. The melted orlistat is allowed to cool at room temperature under reduced pressure till a good crystalline solid is obtained.

In the following section embodiments are described by way of examples to illustrate the processes of the invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Example-1

Preparation of orlistat form II

Orlistat form I (2.0 g) was dissolved in diisopropyl ether (10.0 ml) and stirred at room temperature to get clear solution. The reaction mixture was cooled to 0 to –5°C and the product was precipitated slowly with stirring. The product was filtered and washed with diisopropyl ether. It was then dried at room temperature under vacuum to obtain white crystals of orlistat.
Yield: 1.7 g

XRD, IR spectra and DSC graph were similar to those shown by Fig. 4.5 and 6 respectively, as shown in the accompanied drawings.

Example-2

Preparation of orlistat form I from orlistat form II

2.0 g of orlistat form II was taken and the temperature was raised to 42°C using a water bath to form melted syrup. The syrupy material was dried under reduced pressure to obtain white crystalline orlistat.

XRD, IR spectra and DSC graph were similar to those shown by Fig. 1. 2 and 3 respectively, as shown in the accompanied drawings.

WE CLAIM:

1. A process for preparing crystalline form II of orlistat, comprising crystallizating orlistat from diisopropyl ether.
2. The process according to claim 1, wherein orlistat, obtained as a solution directly from a reaction mixture, is used.
3. The process according to claim 1, wherein amorphous form of orlistat is used.
4. The process according to claim 1, wherein form I of orlistat is used.
5. The process according to claim 1, wherein orlistat is dissolved in diisopropyl ether.
6. The process according to claim 5, wherein the volume of diisopropyl ether is 2 to 10 volume by weight of orlistat.
7. The process according to claim 5, wherein orlistat and diisopropyl ether are stirred at room temperature to get clear solution.
8. The process according to claim 5, wherein orlistat and diisopropyl ether are refluxed to get clear solution.
9. The process according to claim 5, wherein the solution of orlistat in diisopropyl ether is cooled from about 5 to about -20°C to obtain crystals of form II.
10. A process for preparing crystalline form I of orlistat, comprising heating form II of orlistat till it melts and allowing it to cool.
11. A process for the preparation of crystalline form II of orlistat as herein described and illustrated by the examples herein.

Dated 11TH day of September, 2003.

For Ranbaxy Laboratories Limited

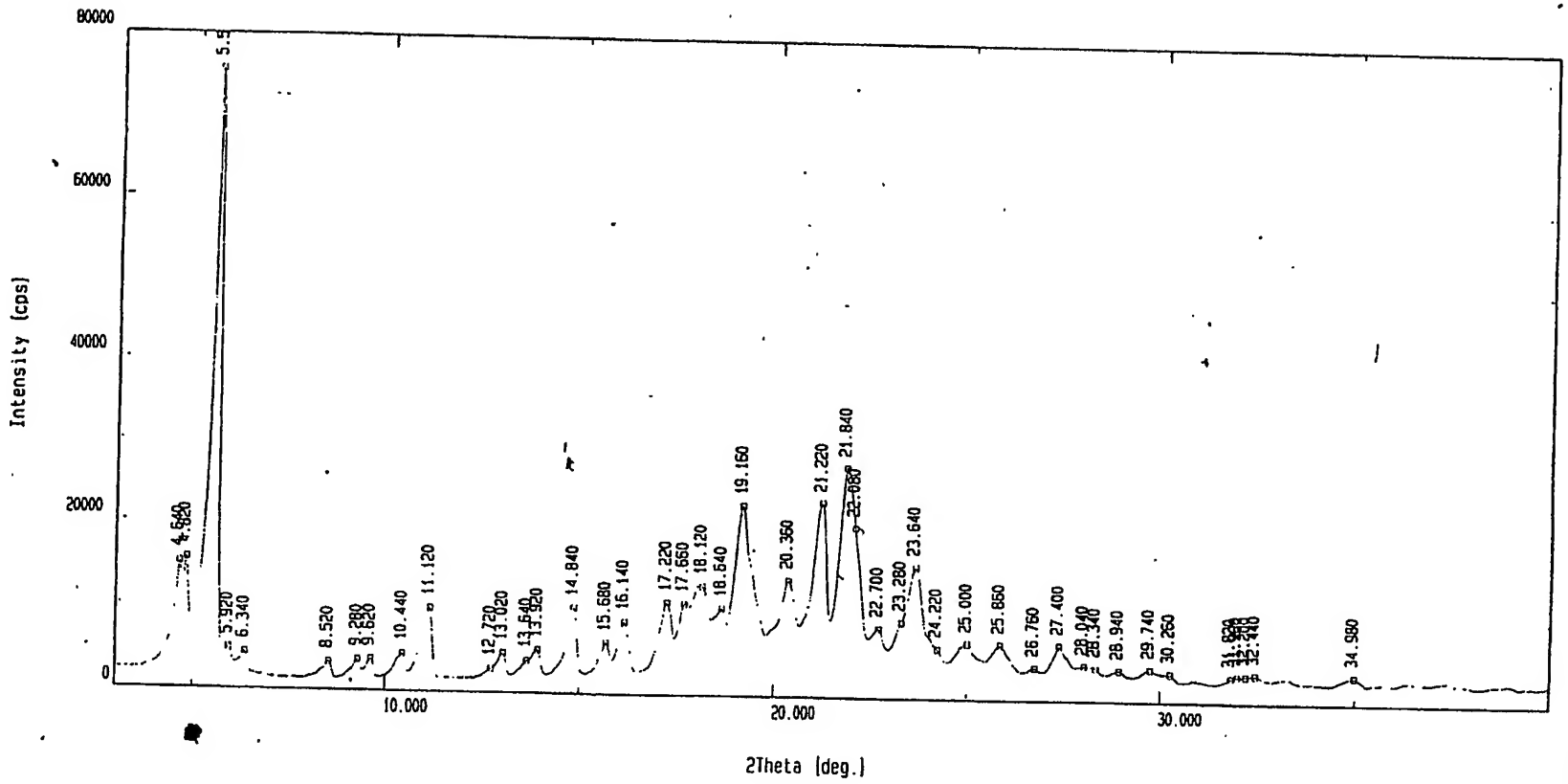
(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

PROCESS FOR PRODUCTION OF CRYSTALLINE FORMS OF OXETANONE DERIVATIVE

A process for preparing crystalline form II of orlistat, is provided. Further a process for preparing the crystalline form I of orlistat from crystalline form II of orlistat. is provided.

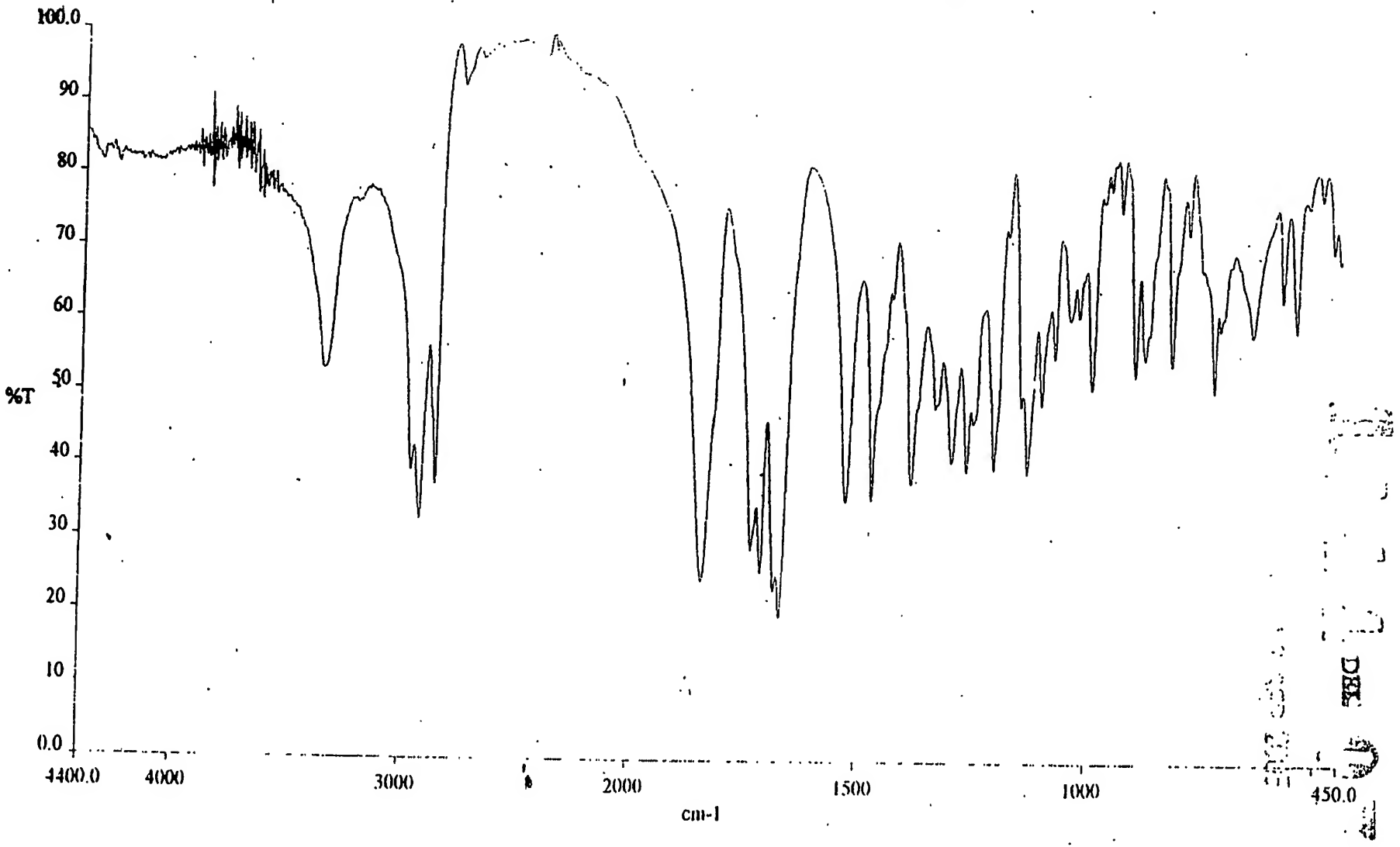
FIGURE 1



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

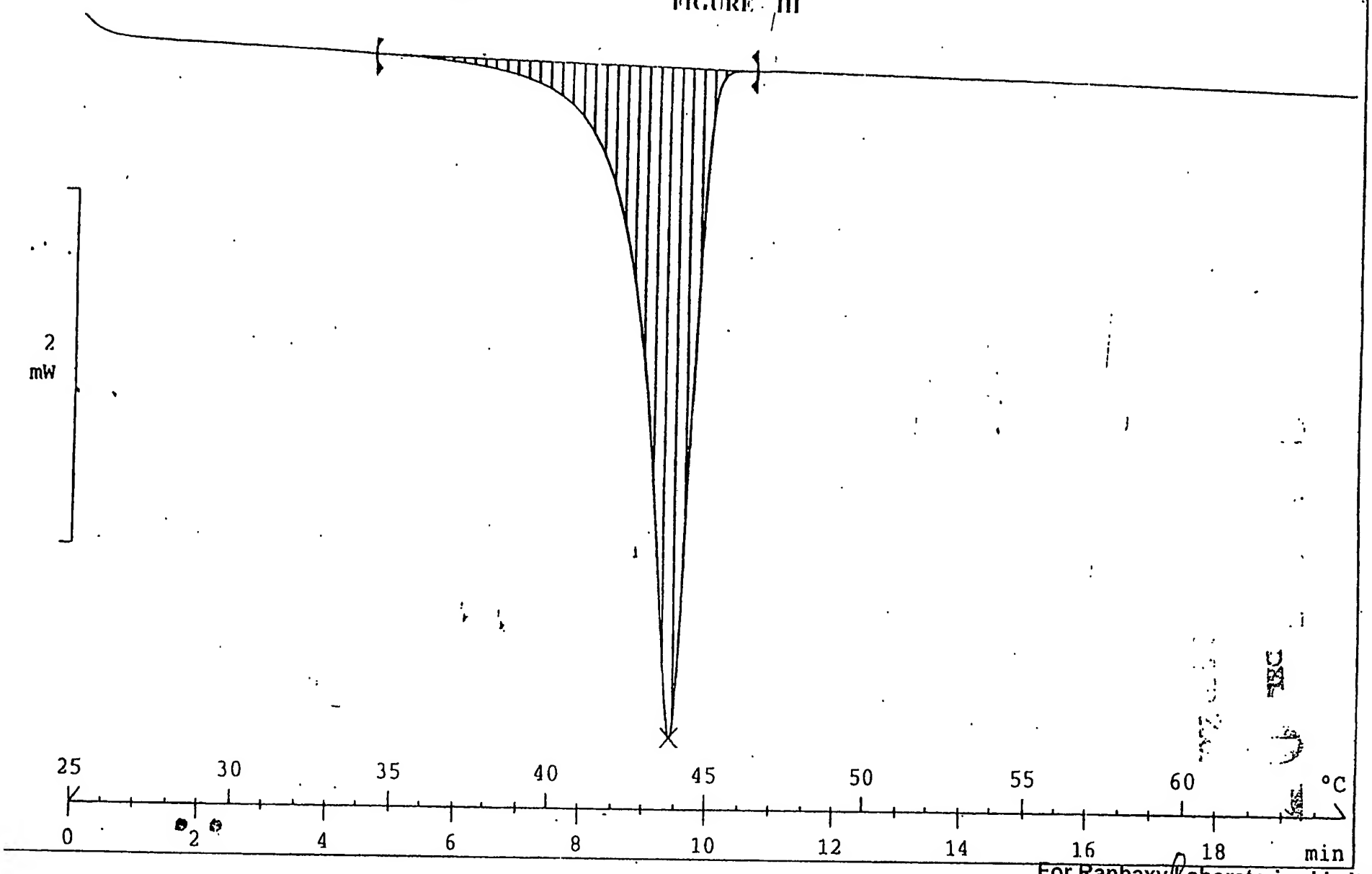
FIGURE – II



For Ranbaxy Laboratories Limited

(Ashish Kumar Patawari)
Company Secretary

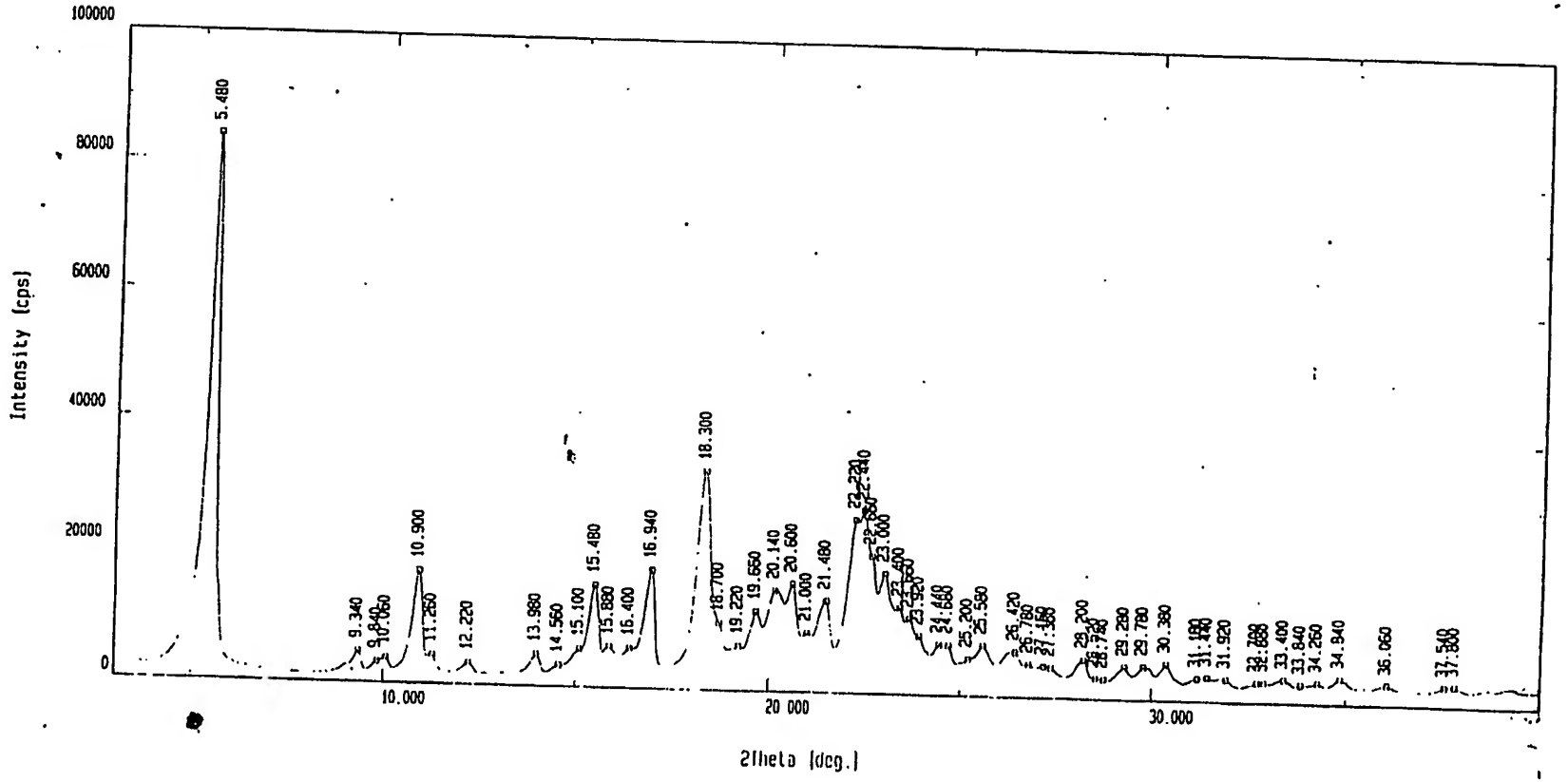
FIGURE - III



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

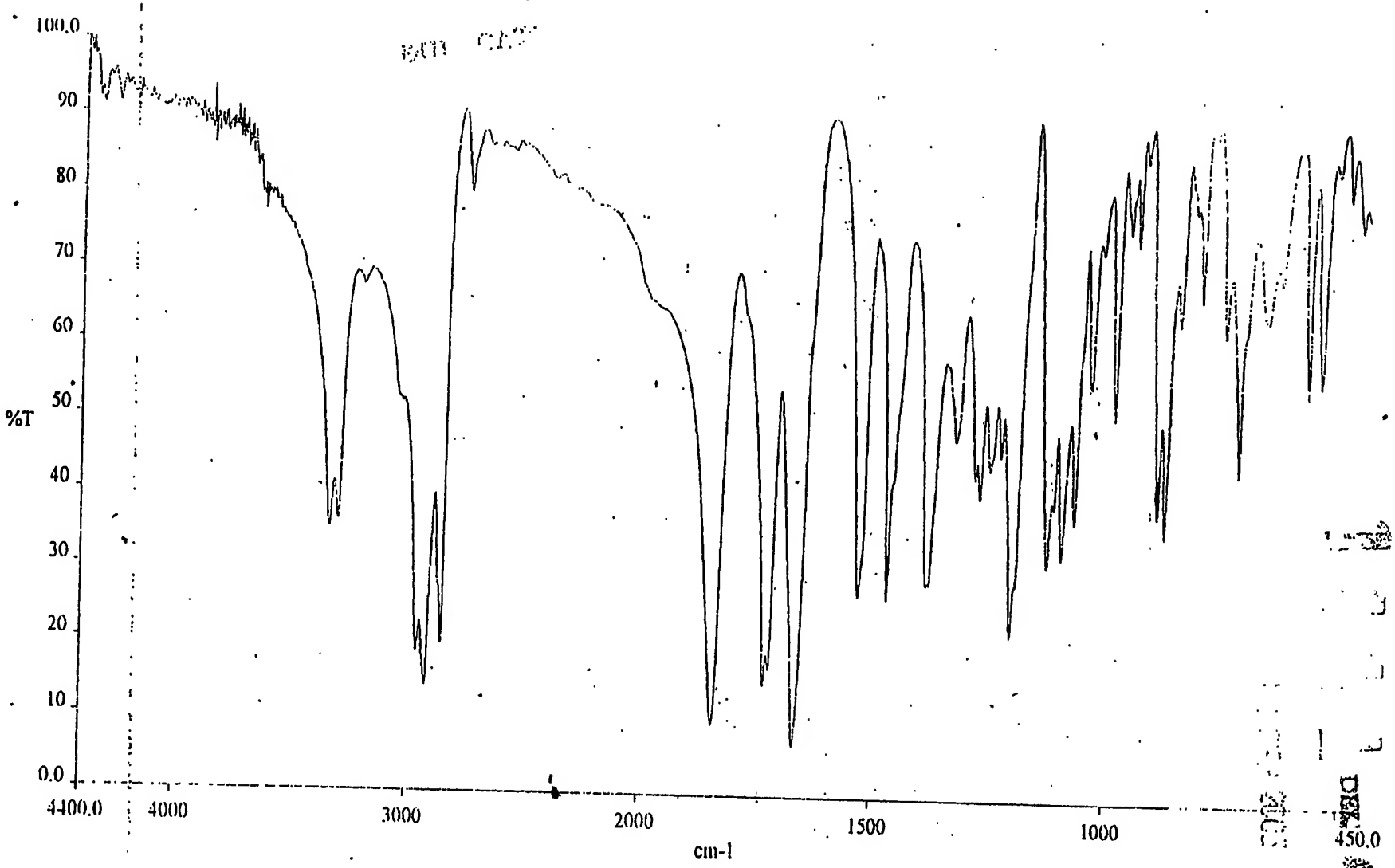
FIGURE – IV



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

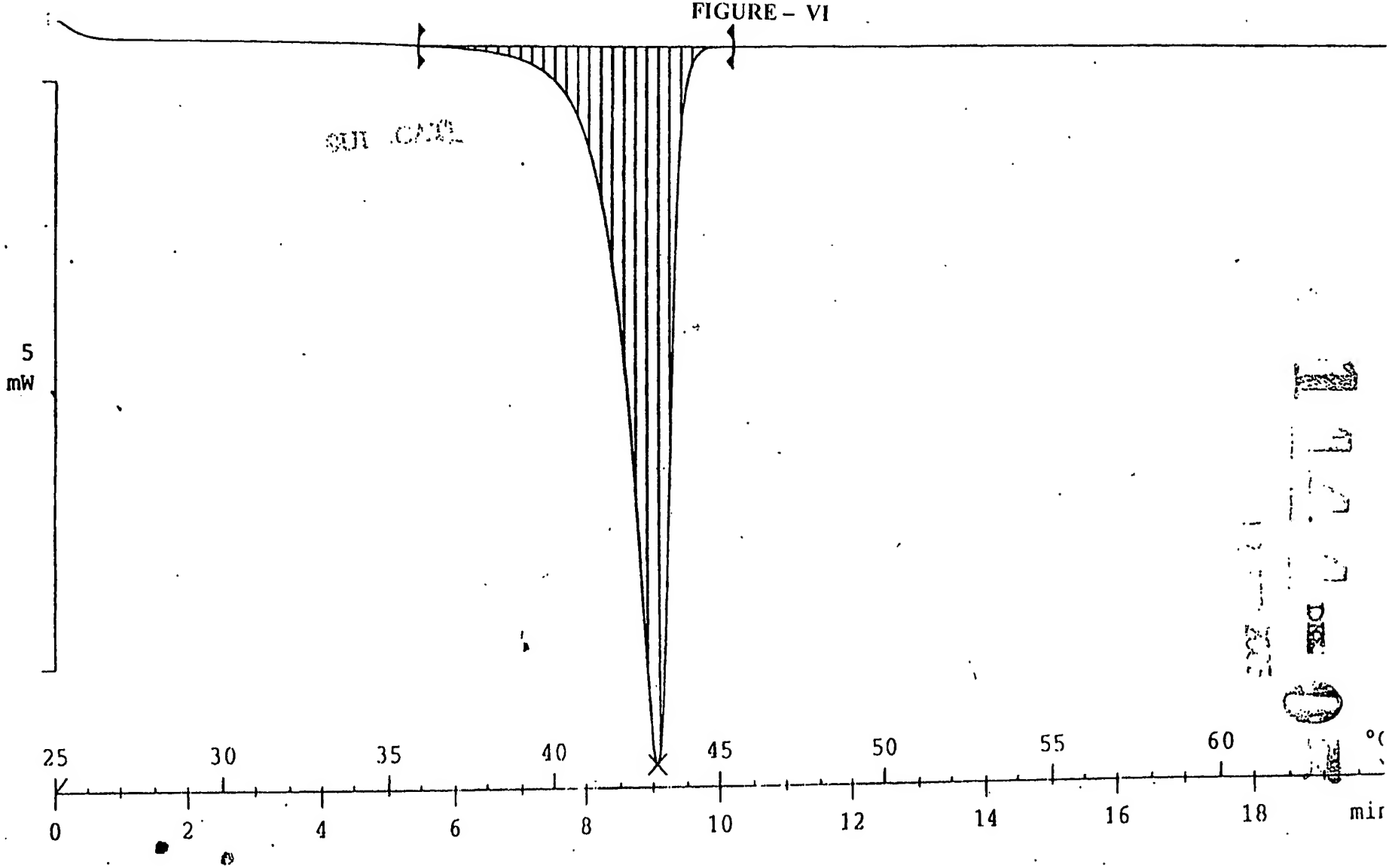
FIGURE V



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE – VI



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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